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Diabetes: Targeting safe and effective prevention and treatment

Ladies and gentlemen:

I am writing to add my thoughts to the proceedings of the NIH/FDA Joint Symposium on Diabetes held on May 13 & 14, 2004. I respectfully request that you include them in the official record.

My interest in endocrinology began in 1986 when I was principal investigator and chief mathematician for Expert Image Systems, a laboratory developing new methods for monitoring and treatment of osteoporosis. My passion for endocrinological research became more focused on October 7, 1988, when my four-year-old daughter Rachel was diagnosed with Type 1 diabetes. Since that day, I have followed in detail every development with the potential to better maintain Rachel's health.

Every diabetic and every parent lives with the nightly fear of hypoglycemia. The unearthly howling of an unconscious child, fallen from her bed, teeth clenched, eyes rolled back, the life ebbing as we struggle to revive her with glucagon injected in the torso and cake icing rubbed into the cheeks, is a nightmare that we know will return, perhaps in a few years, perhaps in a few nights.

Any parent who has seven times brought his child back from death's door must feel the horror of nocturnal hypoglycemia. (Not the full horror - that is for the parents of those who do not survive.) As I review the criteria for clinical and regulatory evaluation of new therapies, no one can think me dismissive of that danger.

But the far greater danger to every Type 1 diabetic is the invisible threat of chronic hyperglycemia. Hyperglycemia does not attack suddenly and dramatically like hypoglycemia. Instead, it eats slowly at the body, silently destroying the eyes, kidneys, feet, blood vessels. Every Type 1 diabetic reasonably expects to be crippled or maimed in some degree, and to die before her time from disease exacerbated by the insidious long-term effects of hyperglycemia. While hypoglycemia offers risk and fear, hyperglycemia offers a near certainty of death or disability.

I got my first education in diabetes treatment from Dr. Joseph Wolfsdorf, chief of pediatrics at Boston's Joslin Diabetes Center and a prominent DCCT investigator. He told every parent that there was no average case of Type 1 diabetes, that every child's needs were different and would be revealed to us day by day and hour by hour. He taught us that we would soon know better than himself or any other clinician how best to care for our child. In the succeeding years, at least a hundred other diabetologists, nurses, diabetes educators, and endocrinology researchers have reconfirmed that wisdom to me.

The job of every patient, clinician, and regulator is simple: to minimize chronic hyperglycemia throughout the decades without excessive added risk of fatal hypoglycemia. Regulators must depend for their judgments on statistical profiles of thousands of patients. Clinicians must depend on charts that show typical responses of each patient at odd intervals. Diabetics and parents can make their discoveries and decisions on the basis of hourly self-measurement and self-observation. It is little wonder that their judgments are usually best.

United States law already trusts diabetics and parents with one of the most dangerous drugs on the pharmacy shelf. Insulin is available in most forms without prescription. We also permit our citizens to select their own activity levels even though carelessly measured physical activity is a major risk factor for hypoglycemia. That is because regulators know what my Rachel's diabetologist knew: that diabetics and parents know, better than physician or regulator can, which risks are right for them, how best to select and measure and balance their insulins and their diet with their daily lives and with the quality of their years to come. To the greatest extent consistent with public safety, the United States should also trust its citizens to make wise daily judgments on the use of the widest range of agents for control of plasma glucose: diet, insulin, pramlintide, sulfonylureas, metformin, exenatide, thiazolidinediones, sports, and other sources of both health and danger.

In 1927, the physicist Walter Heisenberg set forth the principle of uncertainty as an immutable rule of nature. Reduced to common vernacular, it states that measurement of any activity changes that activity so that it cannot be perfectly measurable. For example, the conduct of a public opinion poll must to some extent

shape the public opinion that it is meant only to reflect. Clinical trials of endocrinological agents similarly introduce an uncertainty effect into our data.

The Heisenbergian dilemma is starkly exemplified by the tension between diabetes research and diabetes care. Diabetics learn to balance a wide range of therapies, precautions, and other life choices to best protect their health and quality of life. As they observe the effects of any change in their practices, such as the effects of an added drug on plasma glucose, they properly adjust other parameters such as insulin, activity levels, and nocturnal watchfulness until they reach an optimal balance. Paradoxically, that everyday practice makes it difficult for regulators to separate out the effects of one parameter from another. Each patient knows what works for her, but the regulator cannot easily know the mechanism of action in each case or how one case compares to another. On the other hand, if the trial holds constant all endocrinological agents but one, the more precisely to separate out causes and effects, then the patient is denied the benefit of day-to-day titration for best results. The experiments add one endocrinological agent but remove another, the patient's own judgment; so the resulting suboptimal outcome will understate or conceal the new agent's potential benefits.

While keeping a sharp eye out for every research development that might be applicable to my daughter's health maintenance, I have been following the particular case of pramlintide acetate since 1995. Its trials seem to have been through every possible Heisenbergian permutation. The better it works, the more difficult to view through statistical lenses, and vice versa. But while we statisticians debate the data's meaning for year after year, hundreds of users in open label trials (my Rachel now among them) are living better and healthier lives. When a group of these patients testified before the FDA advisory committee hearings in 2002, they knew better than any clinician how the drug had worked for them. Their pleas to keep a life-enhancing medication brought many listeners to tears.

In 1999, when pramlintide trials overwhelming demonstrated safety and efficacy to patients and clinicians in the dynamic, interactive context of diabetes self-management, its effects were less visible through the traditional prism of static measurements developed for static disease models. As pramlintide faced probable regulatory and commercial extinction, I had the opportunity to give new life to pramlintide (and perhaps to Rachel) through a direct investment in its sponsor; and this experience has led me to support various new medical initiatives in recent years. I feel most fortunate to have been thus able to help develop this therapy for my daughter. Now, to keep it available to her, I must ask regulators to view its effects with the same respect for complexity that Rachel already exercises in pramlintide's daily use.

Glycosylated hemoglobin is frequently referred to as the "gold standard" for regulators of diabetes therapies. In the absence of real-time measurements of plasma glucose, HbA1c has certainly provided a useful suggestive measure for both clinicians and regulators. It alleviates the problem of misreporting by patients, and it indicates the power of some agents to reduce average plasma glucose over a period of months. But finally, an average is only an average. It tells us nothing of the transient lows that can kill our patients suddenly or of the transient highs that can kill them slowly. And it tells us nothing of the improved health and quality of life that can result from modulating plasma glucose, even when the averages come out the same. To understand modern diabetes therapies, we need to look at our glucose every few minutes, not every few months.

When a new agent's effect is to reduce variability in plasma glucose, it becomes just a bad habit, a 20th Century habit, to base our decisions on the mean instead of on the variance. Continuous glucose monitoring is so recent a possibility that there has yet been no opportunity to perform long-range studies on the DCCT scale to measure the outcomes of modulating extremes of plasma glucose. A theoretical purity may suggest that governmental action await that ultimate proof of efficacy. But as our patients' bodies decay, should we not permit them to act on the reasonable judgment that modulated glucose levels must be better, or surely no worse, than the wild swings that may yield similar HbA1c numbers?

As clinicians and regulators, I believe we should humbly admit that our patients, even the most unlettered, are often better clinicians and better regulators – for themselves – than we can ever be. We must not, in excess of caution, prevent our patients from discovering for themselves the best protection that they can devise for their unique bodies and their unique lives. If we must err, and surely we must, then it should be on the side of trusting diabetics and their physicians to perform the only experiment of proven relevance to their unique case.

Sincerely yours,

Allen Andersson
President